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Hypothyroidism in Men in Industry

A Preliminary Report on Chemical Evidence

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• **Of 2,807 specimens from blood donors and men in industry, 340 or 12 per cent had serum protein-bound iodine values of 4.0 micrograms or less per 100 cc.**

In a selected group of 610 "white collar" workers, 52 or 8.5 per cent had similar low values.

Careful reexamination of a sample of the latter group indicated that at least 75 per cent of them had hypothyroidism needing treatment.

Further analysis of the factors producing hypothyroidism and the validation of the incidence found is warranted. If the incidence observed in this study is confirmed, these findings indicate that 6 per cent to 9 per cent, or more than a million middle aged American men have hypothyroidism.

IN THE LAST DECADE of the last century, Osler's textbook[19] was the standard source of information on the diagnosis and treatment of hypothyroidism. Osler credited Sir William Gull[9] and the Ord report[18] with making easy the diagnosis of myxedema proper (adult myxedema, as distinguished from cretinism and cachexia strumipriva). He noted the early use of thyroid gland transplants by Victor Horsley[10] and the subcutaneous injection of an extract prepared first by Horsley's pupil, Murray.[17] A little later, Hector Mackenzie[14] of London and Howitz[11] in Copenhagen started the method of feeding thyroid substance. In Osler's opinion it was well to begin with the powdered gland, one to three grains (0.06 to 0.2 gm.) and gradually increase to ten or fifteen grains (0.6 to 1.0 gm.) daily. "The results," he said, "as a rule are most outstanding—unparalleled by anything in the whole range of curative measures. Within six weeks, a poor, feeble-minded, toad-like caricature of humanity may be restored to mental and body health."

In addition to the clinical types described by Osler, we now recognize juvenile myxedema and hypothyroidism of a degree insufficient to produce myxedematous changes, but associated with other phenomena, in particular delayed skeletal maturation, demonstrably improved by thyroid medication.[36]

Hypothyroidism secondary to hypopituitarism is also a well established entity that more often than not is not of myxedematous degree.[16,24] A low content of protein-bound iodine (PBI) and a low uptake of I^{131} with significant increase of the uptake of I^{131} and output of PBI^{131} following injection of thyrotropin establish the diagnosis.[21] Monotropic deficiency has also been described.[25]

While even before the use of present day procedures it was readily accepted that these nonmyxe-

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dematous forms of hypothyroidism existed, the existence of a common form that the authors and other investigators believe most often represents a state between myxedema and euthyroidism, and which has been defined as "the state of the tissues produced by the presence of less thyroxin than the homeostatic mechanism demands,"[27] has not been generally credited. This form is less easily demonstrable because of dependence on the basal metabolic rate, the cholesterol level and the therapeutic trial as the bases of diagnosis even in this more enlightened day; because of failure to use adequate dosage in therapeutic trials and, finally, because of the weight of tradition, leading textbooks,[4,15,26,37] even to this day, describe only myxedema as it was described by Gull, Ord and Osler more than fifty years ago. They deny or do not mention hypothyroidism. "History may not repeat itself, but the writers of textbooks do and their reiteration, be it true or false, strengthens our beliefs."[2] The feeling of some authorities is that a serum protein-bound iodine of less than 3.5 or 4.0 micrograms per cent 100 cc. (depending on their line of division) may occur in health. The implication is that uncomplaining people are healthy, especially if they have other (indirect) evidence of normal thyroid function, such as the unreliable basal metabolic rate, the nonspecific serum cholesterol or the easily influenced uptake of I^{131}.

We insist that protein-bound iodine below 4 micrograms per 100 cc. of serum indicates a diseased condition that should be treated. Very few exceptions, based on most unusual biochemical mechanisms, occur. These exceptions will be discussed later. One wonders how many uncomplaining obese middle-aged women with fasting blood sugar content of 200 mg. per 100 cc. would be considered healthy, or whether a young woman with hemoglobin content of 10 gm. per 100 cc. of blood would be permitted to go untreated unless she complained of feeling ill. Werner included an extensive description of the changes in myxedema[35] and admonished the reader that lesser grades of the disorder exist.

It has been shown that in usual circumstances the circulating hormone is thyroxin[33] bound chiefly to a globulin (TBG) in the interalpha region in electrophoresis.[7,8] In our experience facilities for determining the serum protein-bound iodine (PBI) content are generally available in California. The test is highly specific and is a reproducible means of directly ascertaining the amount of circulating thyroid hormone.[28,29,34] Before obtaining the specimen of blood or before interpreting the result, certain precautions must be taken, as indeed must be done in the case of many laboratory procedures used in everyday practice. It must be remembed that the iodinated substances used in such roentgenographic studies as bronchograms, myelograms and sinus tract visualization will interfere with determination of PBI for an interminable period of time; the substances used for gallbladder studies and those used for intravenous pyelograms will make the test unreliable for many months or years and for several weeks, respectively. The external application of iodine, the use of iodinated gargles, swabs, toothpaste or suppositories, the ingestion of kelp, mineral-vitamin combinations, potassium iodide, Lugol's solution, expectorants and various other iodinated medicines will also invalidate the test. Use of such substances should be discontinued for three or four weeks before a specimen of blood is drawn. The normal diet, even though it includes seafood and iodinized salt, does not interfere. Administration of a mercurial diuretic causes an artificially low value for 24 to 48 hours when the distillation method is used. Mercury does not obscure the result of the alkaline ash method devised by Barker[1] and modified by Ware.[27] Our laboratory uses the latter procedure with such checks and controls as are necessary to insure reliability.

THE SERUM PROTEIN-BOUND IODINE OF MEN IN INDUSTRY

Through the cooperation of the medical departments of various industries in Southern California and the Hyland Laboratories Blood Bank, 10 cc. specimens of clotted blood drawn at the time of routine examinations were mailed to our laboratory, just as they can be mailed from any remote area to a central laboratory. We have so far determined the protein-bound iodine in duplicate in 2,807 specimens of blood thus obtained. Six hundred and ten of these specimens were drawn at the time of a routine annual physical examination of men who were working in an executive or supervisory capacity —the "white collar group." Most of the men were from 40 to 50 years of age. The results are graphically shown in Chart 1. Delimitation of the normal range of the PBI is not yet finally settled, but the most generally accepted dividing line between euthyroidism and hypothyroidism is 4.0 mcgm. per 100 cc.[3] It had been established that the serum protein-bound iodine does not change with age.[30] There were 340 specimens of the total of 2,807 that contained less than this amount; and in 52 of these the specimens were from the executive group of 610. The incidence of what may be unsuspected or inadequately treated hypothyroidism in men was, then, about 12 per cent for the entire group and 8.5 per cent for the "white collar" group. As to the higher incidence in the blood bank group—all supposedly healthy, not anemic persons, without systemic infection or gross disease—the explanation is not evident and the disparity warrants exhaustive study.

We are at present conducting further studies of

these men aimed at demonstrating the presence or absence of hypothyroidism.

The first such study has been to do a repeat PBI and cholesterol determination on those executives who, on routine screening, were found to have PBI less than 4.0 mcgm. per 100 cc. This was done in 38 instances and the finding was confirmed in 30. Of the eight repeat specimens that were reported normal, four were thought to have become normal because of treatment or more diligent use of previously prescribed thyroid extract. Hence a correct indication of the serum PBI was obtained by the first specimen in 34 of these 38 cases. Twenty-four of the men have had a complete survey that included a history, physical examination, examination of the blood, urinalysis, an electrocardiogram, determination of blood sedimentation rate, of basal metabolic rate, 24-hour uptake of I^{131} and cholesterol content, and, in 12 cases, phospholipid and lipoprotein determinations. The four cases in which the repeat PBI was inexplicably normal are included. The results are summarized in Table 1.

In this selected group it is no surprise that the history was of positive value in only one instance of thyroidectomy. Multiple complaints were admitted, but only that of tiredness or lack of energy was a general one. Fourteen men were overweight at the time of the interview; five others had dieted successfully. Except for a palpable thyroid gland in three cases, there were no helpful physical findings noted. A summary of disorders in which hypothyroidism should be suspected has been published.[31]

Six of the 24 men had previously been diagnosed as hypothyroid. Only three of the six had been taking thyroid extract regularly, and in only two instances was the amount being increased periodically as indicated by serial determinations of PBI. Two were taking a small amount of thyroid extract intermittently. One (Case T, Table 1) had had adequate management some years ago but "friends" advised

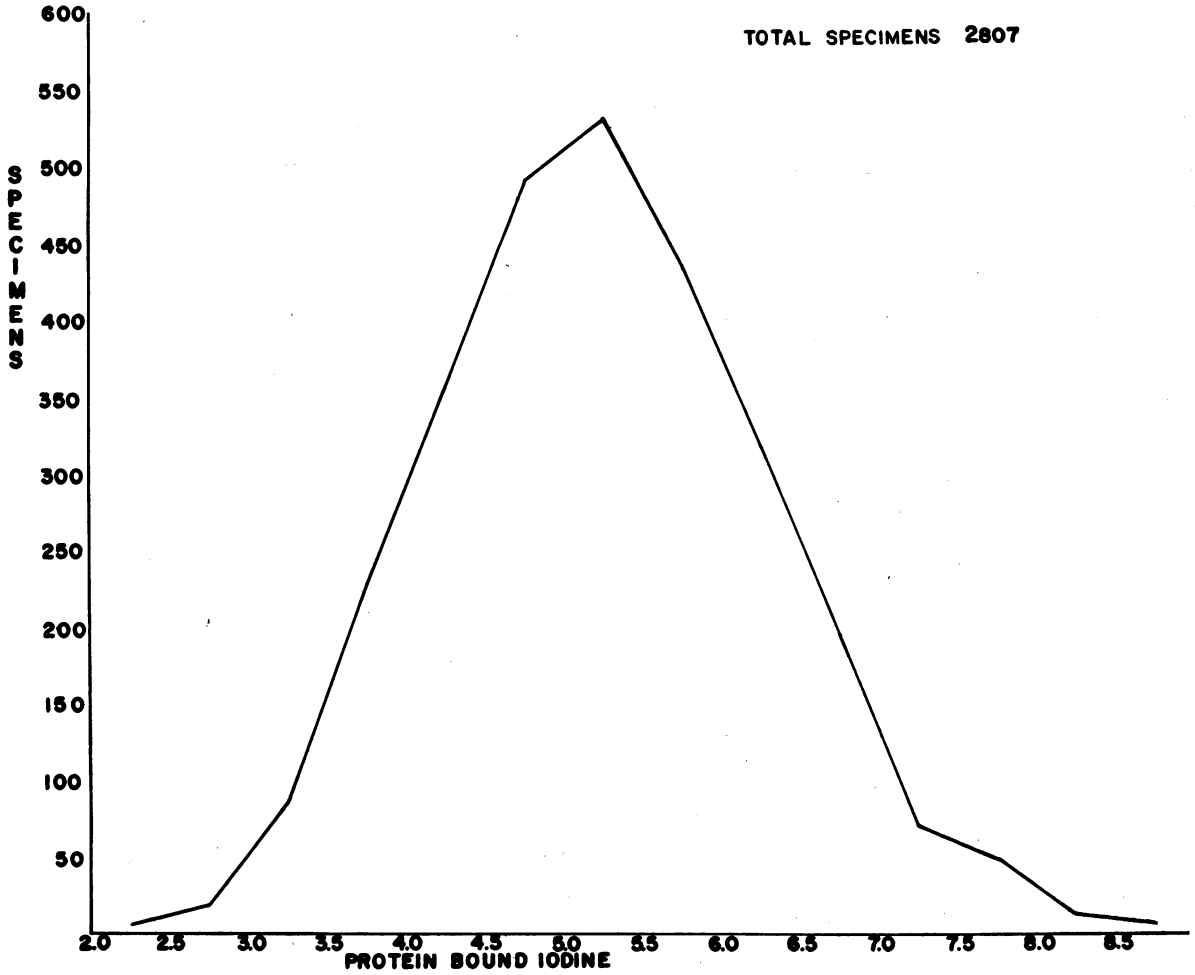

Chart 1.—Arithmetic distribution curve of serum protein-bound iodine values in 2,807 men from about 40 to 60 years of age. The vertical column shows the number of specimens of blood; the horizontal line the content of protein-bound iodine per 100 cc. of serum. The normal range is usually regarded as from 4.0 to 8.0 micrograms per 100 cc. (See Werner, The Thyroid, p. 139, Hoeber-Harper 1955).

TABLE 1.—*Summary of Survey Findings (Twenty-four of Fifty-two Men in the "White Collar" Group)*

Case	Class*	First PBI	Second PBI	BMR	Cholesterol (mg. per 100 cc.)	I^{131} Uptake (Per Cent)	Age (Years)	Comment
A†	II	3.5	3.7	....	190	10.9	23	
B	III	3.0	3.7	— 4	295	12.7	44	
C	IV	3.5	4.5‡	—14	450	1.3‡	56	Taking 0.2 mg. sodium L-thyroxine daily
D	IV	3.7	3.8-4.3	—20	290	14.8	59	Previous thyroidectomy
E	I	3.4	4.5-4.4	— 6	240	15.4	36	
F	IV	3.3	3.9-4.4	—27	230	8.7	48	
G	IV	3.3	3.5-3.9	—12	275	15.1	55	
H	III	3.5	3.5-3.8	+ 4	330	24.1	50	
I	III	2.9	3.4-3.7	— 4	210	2.9‡	55	Taking 0.12 gm. thyroid daily
J	IV	3.6	3.9-3.9	—15	300	6.0	33	
K	IV	3.6	3.5-3.6	—12	270	1.1‡	43	Taking 0.16 gm. thyroid daily
L	IV	3.8	4.2‡	+ 1	350	8.6	43	Taking 0.06 gm. thyroid daily
M	III	3.7	4.0	—11	255	12.7	49	
N	III	3.6	4.1	— 1	350	15.1	57	
O	II	3.6	4.0-4.2	—22	260	17.3	39	Hypometabolism?
P	IV	3.7	5.5‡-5.5‡	—14	310	16.0	41	
Q	II	3.6	3.8-3.8	+ 1	260	19.2	35	
R	II	3.6	4.5-4.7	—20	330	23.2	55	Hypometabolism
S	IV	3.9	4.0-4.2	—17	335	14.7	41	
T	III	2.6	3.3-3.5	— 9	350	13.6	52	Previous treatment
U	IV	3.4	4.4‡-4.6‡	+ 1	310	8.5‡	56	Taking 0.2 gm. thyroid daily
V	II	3.9	4.4-4.6	+ 4	285	18.5	45	
W	III	3.8	3.9-4.0	—14	220	25.6	36	
X	III	3.9	3.9-4.1	+ 7	292	12.4	57	

*Class I, euthyroid; II, probably euthyroid; III, probably hypothyroid; IV, hypothyroid.
†Included because of previous diagnosis of hypothyroidism on basis of low PBI.
‡Effect of treatment.
PBI = Protein-bound iodine, in micrograms per 100 cc. BMR = Basal metabolic rate.

him to stop taking so large a quantity of medicine; later on he had a series of 24-hour I^{131} uptake studies and the results were said to be within normal limits; on this basis and without benefit of such venerated procedures as the determination of basal metabolic rate and cholesterol content, let alone PBI, this man was not taking much-needed thyroid medication.

At this point it should be emphasized that the uptake of I^{131} measures just the ability of the thyroid to accumulate iodine, not its ability to produce or discharge hormone. Of ten men in the present group who were adjudged definitely hypothyroid (Class IV) by virtue of three agreeing tests, four had a low normal uptake of I^{131} (over 10 per cent and under 16 per cent); and of the six with an uptake of less than 10 per cent, four were taking thyroid extract, which might well have suppressed the uptake. In the group considered probably hypothyroid, only one had uptake below 10 per cent, and this person (Case I, Table 1) was taking thyroid extract.

The basal metabolic rate was less than minus 10 per cent in 12 of these subjects, eight of whom were considered as definitely hypothyroid, two probably hypothyroid and two probably euthyroid. In eight of 12 instances when the PBI was 3.5 mcgm. per 100 cc. or below on at least one occasion, the basal metabolic rate was in the normal range. Four of these subjects were considered probably hypothyroid, although they would be definitely considered hypothyroid on the basis of the PBI alone, even with ultraconservative standards. Two men had to be placed in the probable euthyroid group because results of all tests except the PBI were within normal limits. The sources of error in the basal metabolic rate, both inherent and technical, are well discussed by Werner[35] and have repeatedly been emphasized by Starr,[27] whose most interesting observation has been the production of a normal basal metabolic rate in a totally athyreotic myxedematous person, presumably brought about by nervous influences.

An elevated blood cholesterol has long been considered to be of value in the diagnosis of hypothyroidism,[6,12] although Peters and Man[20] were careful to point out that it is even less specific than the basal metabolic rate. A recent study of serum lipids by Jones and co-workers[13] showed that the increase in serum lipids in hypothyroidism is in no way different from that so commonly seen in the metabolic disorders related to overeating and atherosclerosis.

In instances in which there was a sufficient specimen available, we did a cholesterol determination (Chart 2). A control group was taken at random (when there was a sufficient sample available) from the men whose PBI was in the high euthyroid range (6.0 to 8.0 mcgm. per 100 cc.). In the latter group of 138 men, there were 48 men with cholesterol content above 275 mg. per 100 cc. and six with a content below 200 mg. per 100 cc. Of 140 specimens from the group with low PBI, 39 contained more than 275 mg. of cholesterol per 100 cc., but it was some-

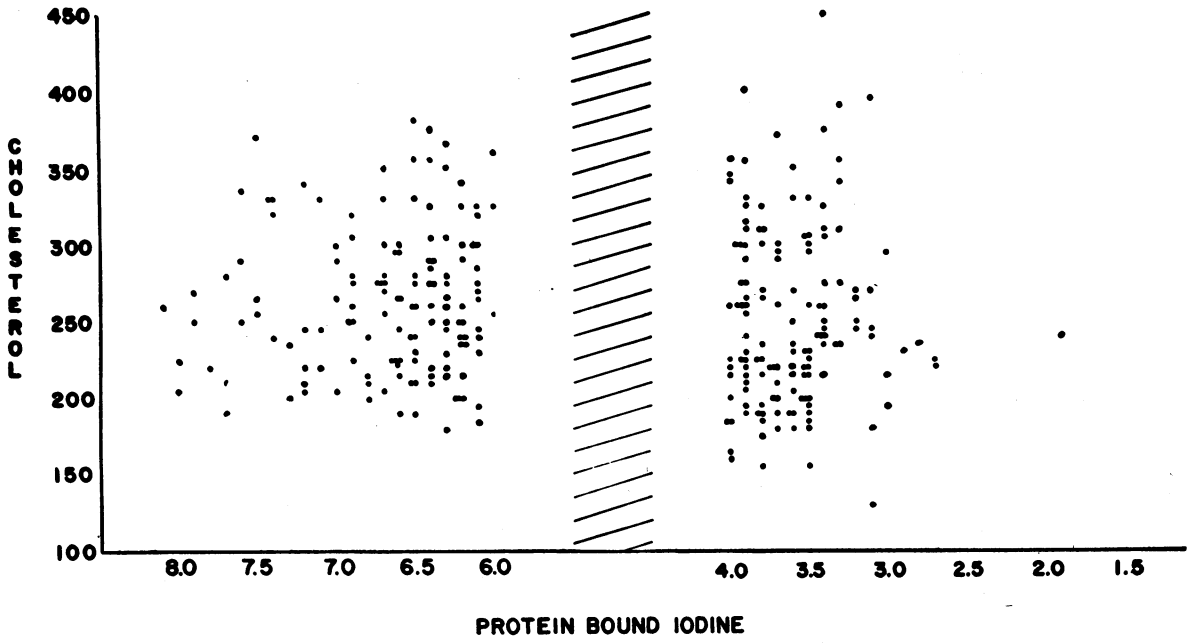

Chart 2.—Serum cholesterol (mg. per 100 cc.) in 138 men with serum protein-bound iodine above 6 micrograms per 100 cc. compared with serum cholesterol of 140 men with serum protein-bound iodine below 4 micrograms per 100 cc.

what surprising to note that 25 had cholesterol below 200 mg. per 100 cc. We have no data as regards the presence of pituitary disease and no additional data regarding thyroid status in this group.

In the selected group of 24 men (Table 1), there was only one with cholesterol under 200 mg. per 100 cc. He was the youngest, leanest man in the group (Case A). In eight other persons considered normal, the range was from 210 to 275 mg. per 100 cc. These included four of the six considered euthyroid or probably euthyroid. Fifteen were found to have cholesterol content above 275 mg. per 100 cc.

The lipoprotein and phospholipid studies provided no data different from that previously reported.[13,20] When total cholesterol is high, phospholipids are also high. The beta lipoproteins ranged from 77 to 91 per cent in 11 of the 12 determinations.

The only electrocardiographic abnormalities were bradycardia and occasional QT prolongation. The hemoglobin and sedimentation rate were within normal limits in all cases.

CLINICAL EVIDENCE OF HYPOTHYROIDISM

On appraisal of these laboratory tests, physical examinations and interviews in 24 men from the 52 in the "white collar" group with low PBI, 18 (75 per cent) were either probably or definitely hypothyroid. They were called probably hypothyroid (Class III) when the repeat PBI was low and the result of one of the other tests was strongly suggestive; they were called definitely hypothyroid (Class IV) when the repeat PBI was low and results of two other tests were highly suggestive. Four of the six adjudged euthyroid were so designated because a repeat PBI was within normal limits; the remaining two had low PBI on repeat test, but no other tests were suggestive of hypothyroidism. Most of these cases (and others as they are detected) will be re-evaluated periodically.

If three quarters of the men with serum protein-bound iodine values of 4.0 micrograms or less per 100 cc. have clinical hypothyroidism, as this study would indicate, the total of American men in the middle-age group with this important deficiency exceeds one million.

Because of individual variation in homeostasis there is no consistent clinical picture in hypothyroidism. The conditions that influence individual response are multiple and subtle. A feeling of well-being may be produced because such adjustments obscure the lack of thyroxin, or vague illness may develop.

Epinephrine, in the presence of small amounts of thyroxin, but not in its total absence,[32] can be a potent synergist of its action. It is possible that it can compensate for thyroxin deficiency.

The effect of the 11-oxygenated adrenal steroids on intermediary metabolism are well documented. Much of their effect is such as to mask thyroxin deficiency. They are particularly capable of restoring normal oxygen consumption even in the absence of thyroxin and of potentiating the effect of small amounts of thyroxin.[5]

It is possible that certain persons have a reduced binding capacity (low thyroxin-binding globulin)

in the serum or an accelerated rate of unbinding, so that a sufficient amount of free thyroxin is available to pass through the capillary walls. It is equally possible that there may be a reduced binding capacity in the extracellular fluid, making sufficient free thyroxin available. In nephrosis where binding capacity may be low, the PBI can be low[22] and yet the needs of the cells are met presumably because the necessary amount of free hormone is available. In normal pregnancy where there is a high thyroxin-binding globulin (TBG) and a high binding capacity,[23] a high PBI, even one of 12 micrograms per 100 cc., is not associated with hyperthyroidism; a PBI of 5.0 micrograms per 100 cc. is regarded as inadequate in pregnancy. There is as yet no demonstration of diminished TBG or increased binding capacity associated with hypothyroidism. Studies of this factor are in progress.

Still another possible explanation is that an enhanced enzymatic conversion of thyroxin to some other metabolically active substance may explain the presence of the normal PBI in these cases.

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